(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 680 401 B1

EUROPEAN PATENT SPECIFICATION

(12)

(45) Date of publication and mention of the grant of the patent:
07.01.1999 Bulletin 1999/01

(21) Application number: 94928996.1

(22) Date of filing: 20.10.1994

(51) Int. Cl.[6]: B29C 45/17, B29C 67/00

(86) International application number:
PCT/IB94/00327

(87) International publication number:
WO 95/12482 (11.05.1995 Gazette 1995/20)

(54) METHOD FOR THE PREPARATION OF PRE-FILLED PLASTIC SYRINGES

VERFAHREN ZUR HERSTELLUNG VON VORGEFÜLLTEN KUNSTSTOFFSPRITZEN

PROCEDE DE PREPARATION DE SERINGUES EN PLASTIQUE PREALABLEMENT EMPLIES

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: 03.11.1993 US 147353

(43) Date of publication of application:
08.11.1995 Bulletin 1995/45

(60) Divisional application:
98108141.7 / 0 862 979

(73) Proprietor:
BRACCO International B.V.
1083 HJ Amsterdam (NL)

(72) Inventors:
- HEFFERNAN, Gayle
Middlesex, NJ 08846 (US)
- WELSHER, Allen
East Brunswick, NJ 08816 (US)

(74) Representative:
Chopard, Pierre-Antoine
c/o BRACCO Research S.A.
7, Route de Drize
1227 Carouge (CH)

(56) References cited:
US-A- 4 718 463

- EUROPEAN PLASTICS NEWS, vol.18, no.8, October 1991 pages 24 - 25 COOKE F. 'Getting started in medical plastics'
- PLASTICS SOUTHERN AFRICA, vol.21, no.4, September 1991 page 10 'Disposable syringes: Klöckner standards for mass production'
- ANTEC 91- CONFERENCE PROCEEDINGS, May 1991 pages 412 - 416 GALIC G. ET AL. 'Molded parts discharged without opening the mold'
- DATABASE RAPRA RAPRA TECHNOLOGY LTD., SHAWBURY, SHREWSBURY, SHROPSHIRE, GB AN : 489025 KIRKLAND C. 'Safer syringes boost moulder opportunities' & PLASTICS WORLD, vol.51, no.8, August 1993 pages 20 - 24
- KUNSTSTOFFE, vol.81, no.9, September 1991, MÜNCHEN pages 768 - 770 ECKARDT H. 'Spritzgiessen im Reinraum'

EP 0 680 401 B1

Printed by Xerox (UK) Business Services
2.16.7/3.6

Description

Field of the Invention

The present invention relates to a novel method for the preparation of pre-filled plastic syringes, and preferably to the preparation of plastic syringes pre-filled with diagnostic contrast agents.

Background of the Invention

Plastic syringes, pre-filled with liquid or semi-solid materials suitable for diagnosis and/or treatment of medical conditions, find utility in the pharmaceutical arts. As can readily be appreciated, it is desirable that such syringes contain minimal amounts of pyrogens and viable and non-viable particulates.

Methods for preparing pre-filled plastic syringes have previously been disclosed. For example, U.S. Patent No. 4,718,463 describes a method for the preparation of pre-filled plastic syringes comprising, among other steps, a step wherein the barrel of the syringe is washed with a multiplicity of jets of water to remove debris and pyrogens from the barrel, followed by assembly and filling of the syringe and a terminal autoclaving step wherein the filled syringe and its contents are sterilized.

In the document EUROPEAN PLASTIC NEWS, 18 [8] (1991), 24-25 (D1), there is disclosed the extrusion molding of medical plastic parts, including disposable syringe bodies and needle hubs under sterile air conditions and under control over contamination by particles from the machine's working parts.

In the document PLASTICS SOUTHERN AFRICA 21 [4] (1991), 10 (D2), there is disclosed the injection molding of polyalkylene disposable syringes under clean room conditions. After the syringes have been assembled from the parts thus manufactured, the completed syringes are sterilized by usual means.

PLAST EUROPE, March 1992, presents an overview of the injection molding under clean room conditions in the general context of various industries suggesting a possibility to achieve clean-room classes 100 and 1000. With respect to class 100 production the article merely states that it can only be achieved under unmanned conditions.

US 5,141,430 discloses an injection molding apparatus which maintains white room environment inside the mold cavity. The apparatus disclosed is said to be suitable for production of digital audio compact disks and for molding of empty medical syringes.

In view of the foregoing, it would be highly desirable to have a method of making prefilled plastic syringes under such clean conditions that final sterilization of the completed and filled syringes be optional.

The method of the present invention, as disclosed in the annexed claims is capable meeting such needs.

Summary of the Invention

Briefly summarized, the method of the invention for making prefilled plastic syringes under conditions substantially free of pyrogen and viable and non-viable particulates, the said syringes including as main components a barrel with a nozzle and an open end opposite said nozzle, a nozzle tip seal, and a piston sliding in the barrel, includes the steps of:

(a) molding suitable plastics into the syringe barrel, nozzle, and tip seal components;
(b) attaching the tip seal to the nozzle;
(c) filling the barrel with injectable diagnostically or medically suitable material;
(d) assembling the piston in the open end of the barrel.

In order to meet the sterility and cleanliness requirements outlined herebefore, at least one of the barrel, nozzle, or tip seal components is molded under class 100 conditions (SI = M3.5) to avoid contamination by non-viable particulates, and under Class MCB-3 conditions or better to avoid viable particulates, i.e. under conditions whereby the level of gram negative microorganisms is less than 88 cfu/m^3 (1 cfu/ft^3).

The method of the present invention, wherein at least one of the aforementioned components, preferably at least the barrel, is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates, allows the preparation of a pre-filled plastic syringe in a less cumbersome and more efficient manner than known methods by obviating the need for subsequent treatment steps such as water washing. Thus, while the component(s) molded under conditions which are substantially free of pyrogens and viable and non-viable particulates may optionally be treated subsequent to molding, such as by water washing, such subsequent steps may be omitted or reduced in intensity or duration by use of the present method.

Preferably, the component(s) molded under conditions which are substantially free of pyrogens and viable and non-viable particulates in accordance with step (a) are maintained under clean conditions until they are assembled in the syringe. In this regard, it is further preferred that clean conditions be maintained at least until the syringe is completely assembled (for example, that the partly assembled syringe be maintained under clean conditions). Thus, in a preferred embodiment, the present invention provides a method for the preparation of a pre-filled plastic syringe, wherein said syringe comprises the aforementioned barrel, tip seal and piston, comprising the steps of:

(a)

(I) providing a barrel which is molded under conditions which are substantially free of pyro-

gens and viable and non-viable particulates, and, providing a tip seal and/or a piston which is also molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and
(ii) maintaining said barrel and, said tip seal and/or piston, under clean conditions for use in step (b); and

(b) filling and assembling said syringe.

In a particularly preferred embodiment, the present invention provides a method for the preparation of a pre-filled plastic syringe, wherein said syringe comprises the aforementioned barrel, tip seal and piston, comprising the steps of:

(a)

(i) providing a barrel which is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates, and, providing a tip seal and/or a piston which is also molded under conditions which are substantially free of pyrogens and viable and non-viable particulates; and
(ii) maintaining said barrel and, said tip seal and/or piston, under clean conditions for use in step (b); and

(b) filling and assembling said syringe, wherein:

(i) the tip seal is attached to the nozzle end of said barrel;
(ii) the barrel and tip seal assembly is filled with a liquid or semi-solid through the open end of the barrel, said open end being opposite said nozzle end of the barrel; and
(iii) the piston is assembled in said open end of the barrel; and

(c) optionally, sterilizing the assembled syringe and its contents.

Brief Description of the Drawings

FIGURE 1 is a sectional view of a pre-filled plastic syringe prepared by the present method.

Detailed Description of the Invention

A preferred configuration of a pre-filled plastic syringe prepared by the present method is illustrated in FIGURE 1. As can be seen from FIGURE 1, the barrel 1 has a nozzle end 2, to which is attached a tip seal 3 and, at the opposite end 4, a plunger (or piston) 5. The piston may be depressed to express the liquid or semi-solid contents 6 of the syringe through the nozzle end.

According to the present method, at least one syringe component, preferably at least the barrel, is molded under conditions which are substantially free of pyrogens and viable and non-viable particulates. The term "molded under conditions which are substantially free of pyrogens and viable and non-viable particulates", as used herein denotes molding under conditions meeting or exceeding SI = M 3.5 (Class 100) conditions with respect to particulates (Federal Standard No. 209E, "Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones, approved by the General Services Administration (Sept. 11, 1992), incorporated herein by reference), and, with respect to microbes, meeting or exceeding Class MCB-3 conditions (*Pharmacopeial Forum*, Volume 18, Number 5, pp. 4048 to 4054, In-Process Revision, The United States Pharmacopeial Convention, Inc. (Sept.-Oct. 1992), incorporated herein by reference), and, in addition, wherein the microbial level of gram negative microorganisms is less than 88 cfu/m^3 (1 cfu (colony forming unit) per cubic foot) of air (and, preferably, also per 30 cm^2 of surface). Class MCB-3 conditions, and/or the aforementioned level of gram negative organisms, may be maintained, for example, by sampling to determine the level of microbes present, and sanitizing or employing other control methods as required (e.g., by surface contact with alcohol, phenolic germicides such as "germ warfare", or chlorite salts such as sodium chlorite salts (e.g., "Expore")). As is understood by one of ordinary skill in the art, "meeting or exceeding" denotes a level of cleanliness which is equal to or greater than the standard referred to.

With respect to particulates, the term "molded under conditions which are substantially free of pyrogens and viable and non-viable particulates", as used herein, preferably denotes molding under conditions meeting or exceeding Class 100 conditions (see the aforementioned Federal Standard No. 209E). With respect to microbes, the term "molded under conditions which are substantially free of pyrogens and viable and non-viable particulates", as used herein, preferably denotes molding under conditions meeting or exceeding Class MCB-2 conditions (see the aforementioned *Pharmacopeial Forum*); and more preferably, conditions meeting or exceeding Class MCB-1 conditions (see the aforementioned *Pharmacopeial Forum*).

In addition to conducting the molding step under conditions which are substantially free of pyrogens and viable and non-viable particulates (that is, under the classified conditions described above), it is preferred to employ an elevated temperature and/or pressure during molding, for example, a temperature and/or pressure where pyrogens, if present, may be partly or completely decomposed during molding. Also, if desired, the starting plastic material may be treated, for example, washed, such as with an aqueous (e.g., water for injection) or organic washing agent and/or sterilized, such as treated with ethylene oxide or irradiated, prior to mold-

ing.

Preferably, as indicated above, a component molded under conditions which are substantially free of pyrogens and viable and non-viable particulates is maintained under clean conditions prior to assembly into the syringe. "Clean conditions" include those defined above for conditions which are substantially free of pyrogens and viable and non-viable particulates, but may also include any art-recognized conditions for maintaining cleanliness such as enclosure in a sealed clean-room bag or wrapper for storage.

A syringe component molded under conditions according to step (a) of the method of the present invention may be provided which is substantially free of pyrogens and viable and non-viable particulates and which is suitable for assembly into a sterile syringe with minimal or no further treatment of the component prior to assembly. Thus, for example, a component such as the barrel molded under the conditions of step (a) of the present method may be assembled into the syringe without water washing. If desired, however, some further treatment may, optionally, be employed subsequent to molding.

In this regard, any of the components of the syringe, including those molded under the conditions of step (a) of the present method, as well as those molded under other conditions ("non-classified conditions"), may optionally be treated by one or more of the following steps subsequent to molding:

(1) blowing the component with a gas, especially with sterile filtered (e.g., filtered through a 0.2μm filter) and/or deionized (facilitating a decrease in the electrostatic attraction of particles to the molded component) air to remove particulate matter;

(2) lubricating the component, such as by treatment with a silicone lubricant;

(3) washing the component with an inorganic (e.g., hydrogen peroxide or water) and/or organic (e.g., freon) washing agent, and, optionally, rinsing the component, such as with water;

(4) sterilizing the component, such as by contact with an antimicrobial agent (for example, hydrogen peroxide (e.g., in liquid or vapor form) or ethylene oxide), by use of radiation (especially, gamma radiation), and/or by autoclaving (such as by use of steam at temperatures of 122 to 124°C and pressures of 33 to 35 psia); and/or

(5) preparing the component for storage or transport, such as by placing the component in a sealed, clean-room bag where it is not to be employed immediately after formation.

Preferred Methods for Preparation of Barrel

The barrel of the syringe may be made of any suitable plastic, and is preferably made of polyolefin, including polyolefin polymers, copolymers and blends, especially polypropylene or blends thereof with polyethylene, or olefin polymers and copolymers including methylpentene, or the like polyolefins.

Preferably, the barrel is injection molded, such as by use of injection molding equipment under conditions known in the art for melting and forming plastics (e.g., injection molding polypropylene pellets into syringe barrels by melting at 400 to 520°F (0.75 to 3 minutes) at 1000 to 1200 psi).

Preferred Methods for Preparation of Tip Seals

The tip seal of the syringe may be made of any suitable plastic, and is preferably made of flexible rubber elastomer such as natural rubber, butyl or halobutyl rubber or blends thereof. The tip seal may be molded, preferably injection or compression molded, such as by use of injection or compression molding equipment under conditions known in the art. The equipment may, for example, be readily selected by one of ordinary skill in the art on the basis of the type of elastomer employed.

Preferred Methods for Preparation of Piston

The piston may be any suitable type, such as a piston operable by a rod or handle for hand injection of the contents of the syringe or a piston operable by a power injector for mechanical injection of the contents of the syringe.

The piston may be made of one, two or more pieces. The piston may, for example, be a single piece component, or a two-piece component consisting of a core and a flexible cover piece attached to or fitting over or onto the core (e.g., allowing the piston to seal the barrel of the syringe). In the latter case, the core is preferably made of a relatively hard plastic such as a polyolefin (e.g., polypropylene) or polycarbonate, and the flexible cover piece is preferably made of a flexible rubber elastomer, such as those materials described above with respect to the tip seal; the two pieces may be preassembled to form the piston prior to insertion into the barrel. Each of the separate pieces of the piston may be molded and optionally treated as described above.

Preferred Methods for Assembly of Syringe

In a preferred embodiment of the present method, the tip seal is assembled by attachment to the barrel, preferably automatically. Filling may then be conducted, such as by use of automatic filling equipment. The syringe may be filled with any suitable liquid (e.g., solution or suspension) or semi-solid (e.g., paste, cream or ointment). Preferably, the syringe is filled with a liquid diagnostic agent suitable for injection, for example, a contrast agent such as ProHance™ (gadoteridol) or Isovue® (iopamidol).

The liquid or semi-solid may then be sealed by insertion of the piston, optionally followed by a terminal

sterilization step. When employed, sterilization is preferably achieved by steam autoclaving. Preferred temperatures for steam autoclaving are those from about 120 to 124°C; preferred pressures are those from about 44 to 53 psia. It is particularly preferred to select a pressure set point so that, under the conditions of the autoclaving, the pressure inside the syringe is approximately in equilibrium with the pressure outside the syringe in the autoclave. An overpressure (pressure outside syringe in autoclave exceeds that in syringe) or an underpressure (pressure in syringe exceeds that outside syringe in autoclave) may, however, also be employed.

In addition to the tip seal, barrel and piston, the syringe prepared by the present invention may include other components, such as any of those known in the art, for example, a handle or rod for the piston, a needle, a protective cap for the needle, and the like.

The following Example further illustrates the present invention, and is not intended to in any way limit the scope of the present claims.

EXAMPLE 1

PREPARATION OF PRE-FILLED PLASTIC SYRINGES

In the following Example, wherever Class 100 conditions are employed, it is understood that the microbial level of gram negative microorganisms is less than 1 cfu (colony forming unit) per cubic foot of air or per 30 cm^2 of surface, and that the conditions meet or exceed Class MCB-3 conditions.

Preparation of Syringe Components

(i) Barrels

Polypropylene resin pellets, prepared by extrusion of a molten 230-270°C (450 to 520°F) polypropylene resin mix (suitable for formation of clear plastic barrels) into pellet form, are pneumatically loaded into a hopper and fed into a sprew. The pellets are then melted at 200-270°C (400 to 520°F) for 0.75 to 3 minutes while under 70 to 84 bar (1000 to 1200 psi). (Methylpentene olefin resin pellets may alternatively be employed, and are preferably dried at 70°C (160°F) for 4 hours prior to being fed into the sprew.)

Under Class 100 conditions (for this and the following steps unless indicated otherwise), the syringe barrels are formed by injection molding of the molten resin, and the formed barrels are picked robotically from the mold. The barrels are optionally blown with 0.2µm sterile filtered, deionised air and/or lubricated with silicone. The barrels are then presented by the robot for visual inspection. A Class 100 molded polycarbonate Luer nut may optionally be machine assembled at this time.

Still under Class 100 conditions, the barrels are matrixed (oriented) into a Class 100 molded polypropylene carrier holder, aligning the barrels for further processing. The barrels may optionally be placed in heat-sealed clean-room bags when stored prior to use. The barrels may also optionally be sterilized, such as by contact with ethylene oxide or by autoclaving. When gas sterilization is contemplated, it is preferred to place the barrels in gas permeable heat-sealed clean-room bags and to sterilize the barrels *in situ*.

(ii) Tip Seals

Halobutyl rubber is compression molded to produce flexible rubber tip seals. Under Class 100 conditions, the tip seals are washed with purified water, United States Pharmacopeia, XXII (1990) (hereinafter, "U.S.P., XXII") which is treated to be pyrogen free or, preferably, water for injection, U.S.P., XXII, optionally siliconized, and optionally placed in heat-sealed clean-room bags when stored prior to use (gas permeable such bags may be employed when gas sterilization, such as by ethylene oxide or autoclaving, *in situ* is desired (see the "Assembly and Fill" section below); such bags may be other than gas permeable if it desired to employ a method of sterilization such as irradiation).

(iii) Pistons

Two-piece pistons are prepared by assembling, preferably mechanically, under Class 100 conditions, an inner hard plastic core and a flexible rubber cover. The pistons may optionally be placed in heat-sealed clean-room bags (preferably, gas permeable such bags when gas sterilization *in situ* is desired) when stored prior to use and/or sterilized, such as by gamma irradiation, or, preferably, by contact with ethylene oxide or by steam autoclaving.

Cores

The cores of the pistons are made from polypropylene (or, alternatively, polycarbonate) molded under the Class 100 conditions described above for molding the barrels. The cores may, alternatively, be molded under non-classified conditions and washed with water for injection U.S.P., XXII or purified water U.S.P., XXII which is treated to be pyrogen free. Optionally, the cores may be placed in heat-sealed clean-room bags (e.g., gas permeable for reasons described above) when stored prior to use.

Covers

The flexible rubber covers are molded under the conditions used to prepare the flexible rubber tip seals, and, under Class 100 conditions, are washed with water for injection U.S.P., XXII or purified water U.S.P., XXII which is treated to be pyrogen free, and siliconized. The flexible rubber covers may optionally be placed in heat-sealed clean-room bags (e.g., gas permeable for rea-

sons described above) when stored prior to use.

Assembly and Fill

The tip seals are sterilized, such as by contact with ethylene oxide or by irradiation or, preferably, by steam autoclaving, and, under Class 100 conditions, are placed into the hopper of a filling machine, and assembled to the barrels. Also under Class 100 conditions, liquid contrast agent, such as Isovue® or ProHance™, is filled into the barrel through the open piston end.

The two-piece pre-assembled pistons, placed into the filling machine hopper, are inserted into the barrels using a vacuum seating mechanism. The filled syringes are steam autoclaved at a temperature between 120 and 124°C and a pressure between 3 and 3.7 bar (44 and 53 psia). Following particulate inspection, the syringes are labeled and packaged for use.

Claims

1. A method for making prefilled plastic syringes under conditions substantially free of pyrogen and viable and non-viable particulates, the said syringes including as components a barrel (1) with a nozzle (2) and an open end (4) opposite said nozzle, a nozzle tip seal (3), and a piston (5) sliding in the barrel, said method comprising

   (a) molding suitable plastics into syringe components (1, 3, 5);
   (b) attaching tip seal (3) to nozzle (2);
   (c) filling the barrel (1) with injectable diagnostically or medically suitable material;
   (d) assembling piston (5) in said open end (4) of the barrel, characterized in that
   (e) in step (a) at least one of components (1, 3, 5) is molded under class 100 conditions (SI = M 3.5) or better in regard to non-viable particulates, and under Class MCB-3 conditions or better in regard to viable particulates, i.e. whereby the level of gram negative microorganisms is less than 88 cfu/m^3 (1 cfu/ft^3).

2. The method of claim 1, wherein said at least one component recited under (e) is the barrel (1) and, optionally, also components (3, 5).

3. The method of claim 2, wherein after step (a), said barrel (1) is maintained under clean conditions and, optionally, also components (3, 5).

4. The method of claim 3, wherein said step (c) is effected by filling the barrel (1) with liquid or semi-liquid through the open end (4) thereof and, optionally, sterilizing the syringe after assembling in step (d).

5. The method of claim 1, wherein said at least one component recited under (e) is molded under conditions meeting or exceeding Class MCB-2 (less than 18 cfu/m^3).

6. The method of claim 1, wherein said at least one component recited under (e) is molded under conditions meeting or exceeding Class MCB-1 (less than 1 cfu/m^3).

7. The method of claim 2, wherein after molding a component of said syringe is treated according one or more of the following steps:

   (i) blowing the component with a gas;
   (ii) lubricating the component;
   (iii) washing the component with an inorganic and/or organic washing agent and, optionally, rinsing the component;
   (iv) sterilizing the component; and/or
   (v) preparing the component for storage or transport.

Patentansprüche

1. Verfahren zur Herstellung vorgefüllter Kunststoffspritzen unter Bedingungen, die im wesentlichen frei vor, Pyrogenen und lebenden und nicht-lebenden Teilchen sind, wobei die Spritzen als Komponenten einen Zylinder (1) mit einer Tülle (2) und ein offenes Ende (4) gegenüber der Tülle, einen Verschluß an der Spitze der Tülle (3), und einen Kolben (5) umfassen, der in dem Zylinder gleitet, wobei man bei dem Verfahren

   (a) geeignete Kunststoffe zu Spritzenbestandteilen formt (1,3,5);

   (b) den Spitzenverschluß (3) an der Tülle (2) anbringt;

   (c) den Zylinder (1) mit injizierbarem, diagnostisch oder medizinisch geeignetem Material füllt;

   (d) den Kolben (5) und das offene Ende (4) des Zylinders miteinander in Verbindung bringt, dadurch gekennzeichnet, daß man

   (e) in Schritt (a) mindestens eine der Komponenten (1, 3, 5) in bezug auf nicht-lebende Partikel unter Klasse 100 Bedingungen (SI= M 3.5) oder besser und in bezug auf lebende Partikel unter Klasse MCB-3 Bedingungen oder besser formt, d.h. wobei der Gehalt an gramnegativen Mikroorganismen kleiner als 88 cfu/m^3 (1 cfu/ft^3) ist.

2. Verfahren nach Anspruch 1, bei dem mindestens ein unter (e) genannte Komponente der Zylinder (1) ist und, gegebenen. falls, ferner die Komponenten (3, 5).

3. Verfahren nach Anspruch 2, bei dem man nach Schritt (a) den Zylinder (1) und, gegebenenfalls, ferner die Komponenten (3, 5) unter sauberen Bedingungen aufbewahrt.

4. Verfahren nach Anspruch 3, bei dem man Schritt (c) durchführt, indem man den Zylinder (1) mit Flüssigkeit oder Halbflüssigkeit durch das offene Ende (4) hindurch füllt und, gegebenenfalls, die Spritze nach Zusammenfügen in Schritt (d) sterilisiert.

5. Verfahren nach Anspruch 1, bei dem mindestens eine der unter (e) genannten Komponenten unter Bedingungen geformt wird, die Klasse MCB-2 (weniger als 18 cfu/m^3) erfüllen oder übertreffen.

6. Verfahren nach Anspruch 1, bei dem mindestens eine der unter (e) genannten Komponenten unter Bedingungen geformt wird, die Klasse MCB-1 (weniger als 1 cfu/m^3) erfüllen oder übertreffen.

7. Verfahren nach Anspruch 2, bei dem man nach dem Formen eine Komponente der Spritze gemäß einem oder mehreren der folgenden Schritte behandelt, bei denen man

   (i) die Komponente mit einem Gas beblast;

   (ii) die Komponente schmiert;

   (iii) die Komponente mit einem anorganischen und/oder organischen Waschmittel wäscht und, gegebenenfalls, die Komponente spült;

   (iv) die Komponente sterilisiert; und/oder

   (v) die Komponente zur Lagerung oder zum Transport herrichtet.

Revendications

1. Procédé de fabrication de seringues préremplies opérant sous conditions pratiquement libres de pyrogènes, ainsi que de particules viables ou non, lesdites seringues comportant comme composants un cylindre (1) muni d'une canule (2) et d'une embouchure (4) ouverte à l'opposé de la canule, un bouchon de canule (3), et un piston (5) coulissant dans le cylindre, ledit procédé comprenant

   (a) le moulage en plastique des composants de seringues;
   (b) la fixation du bouchon (3) à la canule (2);
   (c) le remplissage du cylindre (1) d'une substance injectable médicalement ou diagnostiquement utile;
   (d) l'introduction du piston (5) dans l'embouchure (4) du cylindre (1), caractérisé en ce que (e) à l'étape (a), on moule au moins un des composants (1, 3, 5) sous conditions de classe 100 (SI = M 3,5) ou mieux en ce qui concerne les particules non viables, et sous conditions de classe MCB-3 en ce qui concerne les particules viable, à savoir dans lesquelles conditions le taux de microorganismes gram-négatifs est inférieur à 88 cfu/m^3 (1 cfu/pied^3.

2. Le procédé de la revendications 1, dans lequel le composant choisi mentionné à l'étape (e) est le cylindre (1) et, facultativement, les composants (3, 5).

3. Le procédé de la revendications 2 dans lequel, après l'étape (a), on maintient le cylindre (1) sous conditions propres, de même que, facultativement, les composants (3, 5).

4. Le procédé de la revendications 3, dans lequel on effectue l'étape (c) en remplissant le cylindre (1) par son embouchure (4) d'un produit liquide ou semi-liquide puis, après insertion du piston à l'étape (e), on stérilise facultativement la seringue.

5. Le procédé de la revendications 1, dans lequel on moule le composé choisi à l'étape (e) sous conditions de classe MCB-2 (moins de 18 cfu/m3), ou meilleures.

6. Le procédé de la revendications 1, dans lequel on moule le composé choisi à l'étape (e) sous conditions de classe MCB-1 (moins de 1 cfu/m3), ou meilleures.

7. Le procédé de la revendication 2, dans lequel, après son moulage, on traite un composant de seringue suivant l'un ou plusieurs des stages suivants:

   (i) on projette un jet de gaz sur le composant;
   (ii) on lubrifie le composant;
   (iii) on nettoie le composant au moyen d'un détersif minéral et/ou organique et, facultativement, on le rinçe;
   (iv) on stérilise le composant; et/ou
   (v) on le met en conditions de stockage ou d'expédition

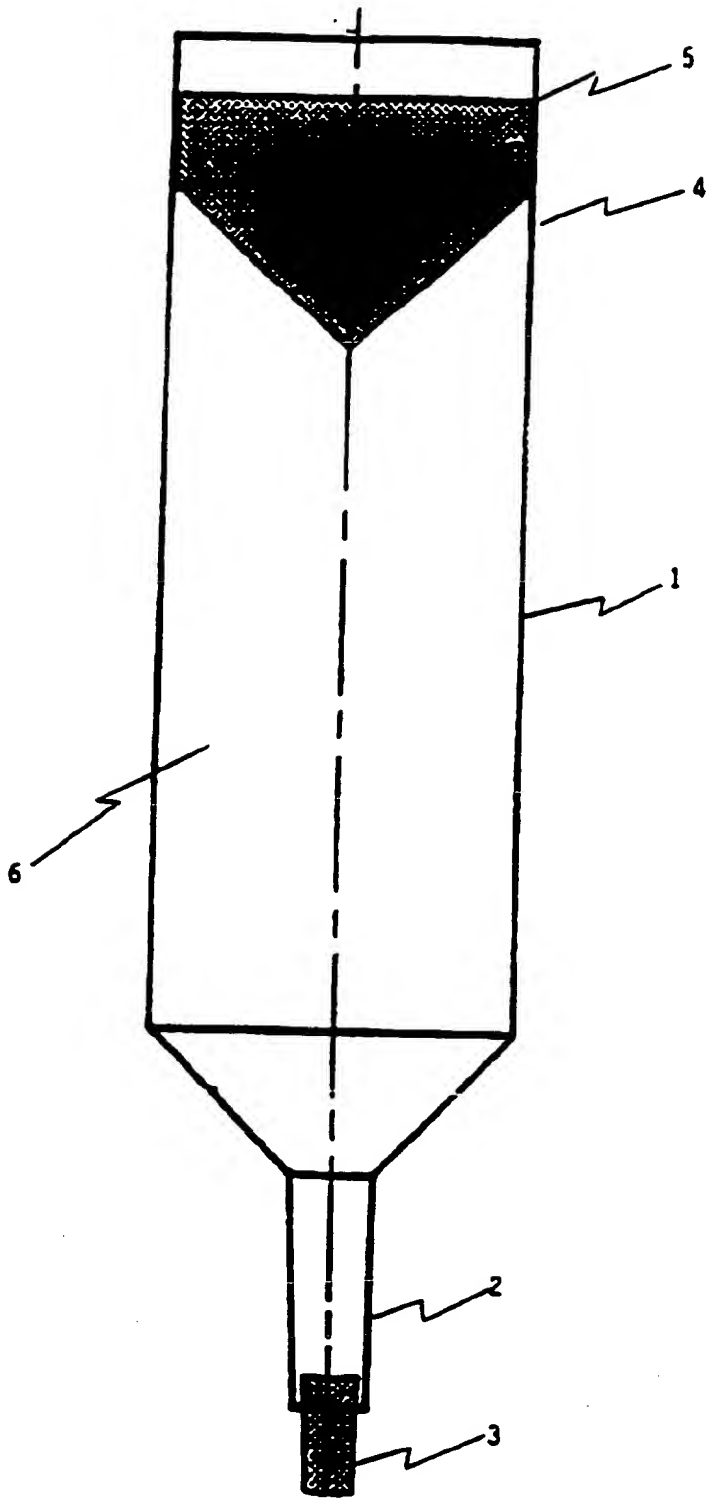

FIGURE 1